UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF PESTICIDE PROGRAMS
Health Effects Division

DEC 18 1996

MEMORANDUM

SUBJECT: Benoxacor: Review of Supplementary Data Package on Benoxacor

TO: Kerry Leifer - Team Leader
Registration Support Branch, Registration Division (7505W)

FROM: David S. Liem, Ph.D. David Sheen 12/10/96
Section II, Toxicology Branch II, HED (7509C)

THROUGH: Clark Swentzel, Section Head K. Clark Swentzel 12/11/96
Section II, Toxicology Branch II, HED (7509C)
and
Yiannakis Ioannou, Ph.D. Y M. Ioannou 12/18/96
Acting Branch Chief, Toxicology Branch II, HED (7509C)

Barcode: D223738; Submission#: S446951; ID#: 7E03489;

MRID#: 433395-01

Chemicals: CGA 154281; Benoxacor

Synonyms: 4-dichloroacetyl-3,4-dihydro-3-methyl-2H-1,4-benzoxazine (CAS# 98730-04-2).

Action Requested: Review a supplemental report regarding the histopathological re-evaluation of the stomach tissues from a subchronic feeding study in rats (MRID#400288-12) that was submitted to the Agency on September 26, 1986. This document should be included with the package sent by HED to RD dated August 29, 1996 (DP Barcode # D223738).

Executive Summary: Based on the histopathological re-evaluation of the stomach tissues, there was a slight diffuse increase in the thickness of keratinized squamous epithelium lining the mucosa of the nonglandular portion of the 6000 ppm rat stomachs. The author considered that the absence of cellular atypia, erosion or ulceration, inflammation or increased mitosis associated with the increased epithelium thickness indicates that this difference is probably not associated with the neoplastic lesions which were noted in the chronic dietary studies in rats and mice. No treatment-related changes were observed at the limiting ridge or in the glandular stomach.

The DER is attached.

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Benoxacor: Subchronic Feeding Study §82-1

Reviewed by: David S. Liem, Ph.D. David Liem 12/10/96
Section II, Toxicology Branch II
Secondary Reviewer: K. Clark Swentzel, Section Head K. Clark Swentzel 12/11/96
Section II, Toxicology Branch II

DATA EVALUATION REPORT

Study Type: Histo-pathological Re-evaluation of the Stomach in a Subchronic Feeding Toxicity Study in Rats

MRID No.: 4333905-01 (original submission MRID#400288-12)

DP Barcode: D223738 SUBMISSION#: S446951 ID#: 7E03489

Test Material: Benoxacor Technical (purity 95%) Synonym: CGA-154281

Dosages: 0, 10, 100, 300, 1000 and 6000 ppm (0, 0.5, 5.0, 15.0, 50.0 and 300 mg/kg/day)

Citation: **Hardisty, J. F., August 2, 1994. Supplement to Subchronic Toxicity Study in Rats (MRID#40028812). Re-evaluation of Stomach** (MRID#433905-01; EPL Inc., Project#140-074).

Action Requested: Review a supplemental report regarding the histopathological re-evaluation of the stomach tissues from a subchronic feeding study in rats (MRID#400288-12). This re-evaluation was conducted because of the concern for fore-stomach tumors that were found in chronic feeding studies using CGA154281 (Benoxacor) in mice (MRID#428887-02) and rats (MRID#428887-04). The rats in the original subchronic feeding study were dosed at dietary levels of 0, 10, 100, 300, 1000 and 6000 ppm (≈ 0, 0.5, 5.0, 15.0, 50 and 300 mg/kg/day) (MRID# 400288-12).

Evaluation Methods: The original slides of the stomach tissues of the 0, 300, 1000 and 6000 ppm dose groups were re-evaluated. The limiting ridge and nonglandular stomach were evaluated separately. The relative degree of severity of inflammatory and degenerative changes were graded on a scale of 1 to 5 (1 = minimal; 2 = Mild/Slight; 3 = Moderate; 4 = Moderately Severe and 5 = Severe/High).

Results: Results of the current stomach histopathological re-evaluation of this study are summarized below:

Incidence	0 PPM 15♂ / 15♀	300 PPM 15♂ / 15♀	1000 PPM 15♂ / 15♀	6000 PPM 15♂ / 15♀
GLANDULAR STOMACH				
-Dilatation, Gastric Gland, Focal	0 / 0	0 / 0	2 / 0	0 / 0
-Inflammation, Focal	0 / 0	0 / 0	0 / 0	1 / 0
LIMITING RIDGE				
-Inflammation	15* / 15	15 / 15	15 / 15	15 / 15
NON-GLANDULAR STOMACH				
-Hyperplasia, diffuse	0 / 0	0 / 0	0 / 0	12 / 9
-Inflammation	0 / 0	0 / 0	0 / 0	1 / 0

All scored a 1 except the Limiting Ridge-Inflammation in one control male (*) which scored a 2; No other scores in this evaluation exceeded 1; Data from p.15-22 of the study report.

No histopathological findings were clearly defined in the original subchronic study submitted in 1986 (MRID#400288-12). It was noted that cell degeneration and necrosis of the pyloric glands were found.

In this current re-evaluation no treatment-related differences were observed at the limiting ridge or in the glandular portion of the stomach of treated rats of either sex as compared to the controls. It was noted that increased thickness of the nonglandular stomach in the 6000 ppm male and female rats was very subtle and only of minimal severity. It should be noted that the mucosa of the nonglandular portion of the stomach in rats is lined by keratinized stratified squamous epithelium; the thickness of the keratin layer varies with age, diet, and degree of distention of the stomach. The author also noted that, in this study, there was no histologic evidence of cellular atypia, erosion or ulceration, inflammation or increased mitosis associated with the increase in thickness of the epithelial layer lining the mucosa of the nonglandular portion of the stomach.
There were no apparent differences in the severity of the inflammatory cell infiltrate (minimal infiltration of eosinophils, neutrophils and occasional mononuclear cell) in the submucosal connective tissue underlying the limiting ridge among the control and treated groups of either sex. The author concluded that the inflammation noted in the glandular portion of the stomach in one 6000 ppm male and in the non-glandular portion of the stomach in another 6000 ppm male rat is not considered to be associated with treatment due to minimal degree of severity and of the low incidence.

Discussion and Conclusions: Based on the above re-evaluation there was a slight diffuse increase in the thickness of keratinized squamous epithelium lining the mucosa of the nonglandular portion of the 6000 ppm rat stomachs. The author considered that the absence of cellular atypia, erosion or ulceration, inflammation or increased mitosis associated with the increased epithelium thickness indicates that this difference is probably not associated with the neoplastic lesions which were noted in the chronic dietary studies in rats and mice. No treatment-related changes were observed at the limiting ridge or in the glandular stomach.